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Article

Use of Straighteners and Other Hair Products and Incident Uterine Cancer

Che-Jung Chang, PhD [1], Katie M. O'Brien, PhD,[1] Alexander P. Keil, PhD,[2] Symielle A. Gaston, PhD,[1] Chandra L. Jackson, PhD,[1,3] Dale P. Sandler, PhD,[1] Alexandra J. White, PhD, MSPH [1,*]

[1]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; [2]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA and [3]Intramural Research Program, National Institute on Minority Health and Health Disparities, Bethesda, MD, USA

[*]**Correspondence to:** Alexandra J. White, PhD, MSPH, Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709-2233 USA (e-mail: alexandra.white@nih.gov).

Abstract

Background: Hair products may contain hazardous chemicals with endocrine-disrupting and carcinogenic properties. Previous studies have found hair product use to be associated with a higher risk of hormone-sensitive cancers including breast and ovarian cancer; however, to our knowledge, no previous study has investigated the relationship with uterine cancer. **Methods:** We examined associations between hair product use and incident uterine cancer among 33 947 Sister Study participants aged 35-74 years who had a uterus at enrollment (2003-2009). In baseline questionnaires, participants in this large, racially and ethnically diverse prospective cohort self-reported their use of hair products in the prior 12 months, including hair dyes; straighteners, relaxers, or pressing products; and permanents or body waves. We estimated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) to quantify associations between hair product use and uterine cancer using Cox proportional hazard models. All statistical tests were 2-sided. **Results:** Over an average of 10.9 years of follow-up, 378 uterine cancer cases were identified. Ever vs never use of straightening products in the previous 12 months was associated with higher incident uterine cancer rates (HR = 1.80, 95% CI = 1.12 to 2.88). The association was stronger when comparing frequent use (>4 times in the past 12 months) vs never use (HR = 2.55, 95% CI = 1.46 to 4.45; P_{trend} = .002). Use of other hair products, including dyes and permanents or body waves, was not associated with incident uterine cancer. **Conclusion:** These findings are the first epidemiologic evidence of association between use of straightening products and uterine cancer. More research is warranted to replicate our findings in other settings and to identify specific chemicals driving this observed association.

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Uterine cancer is one of the most common gynecologic cancers. Overall, incidence and mortality rates have increased in the United States in the past 2 decades, with more than 65 950 new cases and 12 550 deaths expected in 2022 (1,2). Exposure to excess estrogen and a hormonal imbalance of estrogen and progesterone have been identified as key risk factors for uterine cancer (3,4). Thus, it has been hypothesized that synthetic estrogenic compounds such as endocrine-disrupting chemicals (EDCs) could contribute to uterine cancer risk because of their ability to alter hormonal actions (5-11).

Hair product use, a predominant exposure pathway to various EDCs (12,13), has been associated with hormone-sensitive cancers including breast (14-19) and ovarian cancer (20-23) in previous epidemiologic studies. Hair product constituents, including formaldehyde (24-27) and formaldehyde-releasing chemicals (28-30) in some straighteners, and oxidized para-phenylenediamine and 4-aminobiphenyl in hair dyes (25,31-33), have also played a potential role in carcinogenesis, supporting an association between hair product use and cancer development.

Hair product use is common among women in the United States and Europe with more than 50% reporting ever using permanent hair dyes (19,22,34). In the Sister Study, we have previously observed a higher breast cancer incidence associated with adolescent (18) and adult use (19) of hair products and a higher ovarian cancer incidence associated with adult use of straighteners (22). However, to our knowledge, no study has investigated the influence of hair product use on uterine cancer. Therefore, this study aims to examine associations between hair product use and the age-specific hazard of uterine cancer in a large, racially and ethnically diverse cohort in the United States.

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Methods

Study Population

The Sister Study is a prospective cohort that enrolled 50 884 women in 2003-2009. Participants were eligible if they were breast cancer–free women aged 35-74 years who had at least 1 sister diagnosed with breast cancer and if they lived in the United States, including Puerto Rico (35). At baseline, participants completed an interview and self-administered questionnaires that included questions about hair product use. Weight and height were measured during a home visit at baseline by trained examiners. Participants or next of kin for deceased participants are contacted annually for health updates regarding new cancer diagnoses and other health-related changes, and every 2-3 years for more detailed follow-up assessments. Response rates have been near 90% throughout follow-up (36). Data for the current analysis included person-time through September 2019 (Data Release 9.1). Written informed consent was obtained from all participants. This study is overseen by the institutional review boards of the National Institutes of Health.

We excluded women who withdrew from the study (n = 3), who self-reported a diagnosis of uterine cancer before enrollment (n = 380), had an uncertain uterine cancer history (n = 10), had an unclear timing of diagnosis relative to enrollment (n = 59), had a hysterectomy before enrollment (n = 15 585), who did not answer any hair product use questions (n = 736), and who did not contribute any follow-up time (n = 164), resulting in 33 947 eligible women.

Exposure Assessment

At baseline, participants were asked to complete a questionnaire on hair product use in the previous 12 months. Participants reported their frequency of personal use (application by themselves or others to their own hair) of 7 hair products including permanent, semipermanent, and temporary hair dyes; bleach; highlights; straighteners, relaxers, or pressing products; and hair permanents or body waves with the response options including "did not use," "1-2 times per year," "every 3-4 months," "every 5-8 weeks," "once per month," and "more than once per month." Additionally, frequency of nonprofessional application to others was collected for permanent hair dyes, semipermanent hair dyes, and straighteners, relaxers, or pressing products. Based on exposure distribution, we collapsed frequency variables as no more than 2 and more than 2 times per year for hair permanents and as no more than 4 and more than 4 times per year for the other hair product use among ever use. These exposure variables were also dichotomized to never and ever use. Color of dyes ("dark," "light") and lifetime duration of use ("did not use," "less than 5 years," "5-9 years," "10 or more years") were obtained for permanent and semipermanent hair dye use.

Outcome and Covariate Assessment

Uterine cancer cases were defined as women who reported a diagnosis of endometrial cancer, uterine sarcoma, or other types of cancer in the uterus after enrollment (n = 378). Women reporting a cancer diagnosis were asked to provide authorization to retrieve medical records. A total of 262 (69.3%) cases were confirmed using either medical records (n = 247) or death certificates indicating the primary or underlying cause of death as uterine cancer (n = 15). For those without medical confirmation, the information was obtained through self-report (n = 109) and next of kin (n = 7). The positive predictive value of self-reported uterine cancer cases in relation to medically confirmed cases is 85%.

Of 262 medically confirmed uterine cancer cases, 248 (94.7%) were classified as endometrial cancers using *International Classification of Disease*–10 code C54.1. Further, we used *International Classification of Disease*–Oncology-3 histology codes to define type I and type II endometrial cancer (37). Type I endometrial cancers are more hormone sensitive with greater estrogen receptor expression and tend to have better outcomes and survival, whereas type II cancers tend to be more clinically aggressive and have a poor prognosis (38-41).

Other covariates collected at baseline included self-reported age, race and ethnicity (African American/Black including Hispanic/Latina, Hispanic/Latina non-Black, non-Hispanic White, and all others, including Asian/Pacific Islander or American Indian), physical activity (metabolic equivalent hours per week), smoking status (never, past, or current), alcohol consumption (never or past, current <1 drink per day, current ≥ 1 drink per day), educational attainment (high school or less, some college, college and above), and occupational history working in beauty salons or barbershops. Reproductive history included age at menarche (younger than 13 years, 13 years and older), menopausal status (premenopausal and postmenopausal), parity (0, 1, 2, ≥ 3), oral contraceptive use (none, <2, 2 to <10, ≥ 10 years), hormone replacement therapy use (none, estrogen alone, estrogen plus progesterone but never estrogen alone). Body mass index (BMI) was calculated by height and weight measured at baseline (35).

Statistical Analysis

We estimated pairwise correlations using Spearman correlation coefficients among frequency metrics for hair product use. Associations between hair product use and uterine cancer were assessed using Cox proportional hazards models with age as the timescale. Women were followed from enrollment until uterine cancer diagnosis and were considered censored at the earliest event including hysterectomy, loss to follow-up, death, or end of follow-up. The 95% confidence intervals (CIs) were calculated using cluster-robust sandwich estimators to account for relations among participants (2872 women had >1 family member enrolled). Cox models were adjusted for an a priori selected list of confounders including race and ethnicity, educational attainment, BMI (restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentile, kg/m^2), physical activity, menopausal status at enrollment, parity, smoking status, alcohol consumption, oral contraceptive use duration, hormone replacement therapy, and age at menarche. Proportional hazards assumptions were evaluated by Wald tests of covariate-by-attained-age interaction terms. P_{trend} was assessed using Wald tests for continuous variables of hair product use frequency and duration.

We considered whether associations between hair product use and uterine cancer varied by race and ethnicity, obesity, and physical activity. Stratum specific hazard ratios (HRs) were estimated by augmenting our primary model with hair product-by-modifier interaction terms, and heterogeneity was tested using Wald tests. Hazard ratios by race and ethnicity were only estimated for African American/Black and non-

Hispanic White participants because of the small number of women in other racial and ethnic groups. To estimate the cumulative risk of developing uterine cancer by age 70 years, we used the Breslow method to create baseline hazard functions for uterine cancer and competing risks, and a modified Aalen-Johansen estimator for cumulative risk for all participants, standardized to the covariate distribution of the study population (42). From this, we calculated absolute differences and numbers needed to harm for use of straighteners.

We also evaluated the associations by different cancer subtypes, including pre- and postmenopausal uterine cancers, endometrial cancer, and types I and II endometrial cancers. Women who were premenopausal at enrollment were at risk for premenopausal uterine cancer until menopause, at which time they were considered at risk for postmenopausal uterine cancer. Women became at risk for postmenopausal uterine cancer at either age at enrollment or age at menopause, whichever was later.

Several sensitivity analyses were conducted to evaluate the robustness of our findings. First, we restricted the outcome to medically confirmed uterine cancer cases. Second, we removed physical activity from the model because physical activity may act as a confounder and/or a mediator. Costly and time-consuming hairstyling practice may be a barrier to physical activity, whereas women engaging in intense physical activities may change their hairstyling practices (43,44). We excluded 1048 women who had worked in beauty salons or barbershops to eliminate the potential impact of occupational exposure. We considered simultaneous adjustment for other personal hair product use, including frequently used products and all products. Further, the first year of follow-up was excluded to assess the possibility of reverse causation. Finally, associations with use of straighteners or hair permanents as a combined exposure were estimated because these terms have been used interchangeably in African American and/or Black communities to describe chemical products used to change the texture of hair (45,46).

Because of sample size limitations, the frequency, stratified, and sensitivity analyses are only reported for the products more frequently used, including personal use of permanent dyes, semipermanent dyes, straighteners, and hair permanents. Estimates with fewer than 5 cases in any stratum in the statistical model are not reported. Complete-case analyses were done with 557-1316 (1.6%-3.9%) women being excluded in the main analyses because of missingness in any variable. All analyses were conducted in R version 4.1.0.

Results

We followed participants for a mean of 10.9 years. The study population consists of 7.4% Black/African American, 4.4% Hispanic/Latina non-Black, 85.6% non-Hispanic White, and 2.5% all other race and ethnicity. Participants had high educational attainment on average (55.8% college degree or above). Compared with the cohort overall, uterine cancer cases tended to be older with an earlier age at menarche, a higher BMI, and lower physical activity (Table 1). The participants who ever used straighteners were mostly African American/Black (59.9%) and tended to be younger with a higher BMI and lower physical activity than those never used (Supplementary Table 1, available online). The frequencies of use of different hair products were weakly correlated with each other (correlation coefficients: −0.10 to 0.39).

We observed an 80% higher adjusted hazard of uterine cancer among women with ever straightener use in the previous 12 months (HR = 1.80, 95% CI = 1.12 to 2.88) (Table 2). There was a monotonic exposure-response relationship with increasing frequency of use of straighteners (P_{trend} = .002) (Table 3). Compared with no use, infrequent straightener use (≤4 times per year) was associated with an elevated but not statistically significantly higher rate of uterine cancer (HR = 1.20, 95% CI = 0.63 to 2.29), whereas for frequent use (>4 times per year), the hazard ratio was 2.55 (95% CI = 1.46 to 4.45). Among women who never used straighteners in the 12 months prior to baseline, approximately 1.64% were predicted to develop uterine cancer by age 70 years. The estimated risk was 1.18% (95% CI for risk difference = 0.15% to 2.54%) higher for the women with ever use, and 2.41% (95% CI for risk difference = 0.52% to 4.80%) higher for those with frequent use compared with never use. The numbers needed to harm were 85 and 42 for the women with ever and frequent straightener use, respectively—that is, one additional uterine cancer case would be expected for every 85 ever users or every 42 frequent users. In contrast, use of other hair products, including permanent hair dye, was not associated with an increased rate of uterine cancer (Tables 2 and 3).

The observed higher rates of incident uterine cancer with straightener use remained evident when restricting the outcomes to postmenopausal (frequent use: HR = 2.52, 95% CI = 1.39 to 4.55) cases and medically confirmed uterine (frequent use: HR = 2.78, 95% CI = 1.39 to 5.55) and endometrial (frequent use: HR = 2.68, 95% CI = 1.30 to 5.53) cancer cases (Table 4). Further, we categorized endometrial cancer to type I (n = 199; 80.2%) and type II (n = 40; 16.1%) tumors. The association for straightener use was again similar for type I endometrial cancer (frequent use: HR = 2.94, 95% CI = 1.42 to 6.08). Because of the small number of premenopausal and type II endometrial cancer cases, we were unable to reliably estimate associations for some products.

We observed heterogeneity by physical activity, with stronger estimated associations of straightener use among women reporting low levels (<33rd percentile: 32.7 metabolic equivalent hours per week) compared with high levels (≥33rd percentile; ever use $P_{heterogeneity}$ = .05; frequent use $P_{heterogeneity}$ = .09) (Table 5). Among ever use, the hazard ratios were 2.59 (95% CI = 1.46 to 4.61) and 1.30 (95% CI = 0.71 to 2.38) in women with low and high physical activity, respectively. Similar patterns were also observed among women with frequent use (low physical activity: HR = 3.72, 95% CI = 1.91 to 7.25; high physical activity: HR = 1.86, 95% CI = 0.89 to 3.87). Hazard ratios of straightener use did not vary by race and ethnicity or obesity. Moreover, no hazard ratio modification by physical activity, race and ethnicity, or obesity was observed for use of permanent dyes, semipermanent dyes, or hair permanents (Supplementary Table 2, available online). Results of our sensitivity analyses did not indicate any major departure from the results of the main analysis (Supplementary Table 3, available online).

Discussion

In this large, prospective US-based cohort, we observed novel findings of a higher incident uterine cancer rate for women who self-reported either ever or frequent hair straightener use in the 12 months prior to the baseline, relative to those who did not. Negligible associations were observed for other hair products used including permanent dyes, semipermanent dyes, temporary dyes, bleach, highlights, and hair permanents with uterine

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Table 1. Characteristics of the study participants in the Sister Study at enrollment by incident uterine cancer cases, 2003-2009

Chrarcteristics[a]	Incident uterine cancer cases (n = 378)	Full eligible cohort[b] (n = 33 947)
Mean age (SD), y	58.0 (8.07)	54.2 (8.94)
Mean follow-up time (SD), y	6.45 (3.61)	10.9 (3.08)
Mean age at menarche (SD), y	12.4 (1.40)	12.7 (1.51)
< 13 years old, No. (%)	196 (51.9)	15 570 (45.9)
Race and ethnicity, No. (%)		
African American/Black including Hispanic/Latina Black	29 (7.7)	2523 (7.4)
Hispanic/Latina non-Black	14 (3.7)	1508 (4.4)
Non-Hispanic White	326 (86.2)	29 060 (85.6)
Other	9 (2.4)	854 (2.5)
Education, No. (%)		
High school or less	47 (12.4)	4523 (13.3)
Some college	119 (31.5)	10 482 (30.9)
College or above	212 (56.1)	18 937 (55.8)
Mean body mass index (SD), kg/m^2	30.4 (7.2)	27.3 (6.1)
Normal or underweight, No. (%)	91 (24.1)	14 408 (42.4)
Overweight, No. (%)	109 (28.8)	10 453 (30.8)
Obese, No. (%)	178 (47.1)	9075 (26.7)
Mean physical activity (SD), metabolic equivalent (MET) hours per week	47.7 (32.7)	50.8 (31.3)
Low (<33rd percentile 32.7 MET hours per week), No. (%)	146 (38.6)	11 114 (32.7)
Premenopausal, No. (%)	103 (27.2)	14 108 (41.6)
Parity, No. (%)		
Nulliparous	82 (21.7)	6769 (19.9)
1 birth	51 (13.5)	5033 (14.8)
2 births	145 (38.4)	12 472 (36.7)
≥3 births	99 (26.2)	9650 (28.4)
Smoking status, No. (%)		
Never	195 (51.6)	19 370 (57.1)
Past	166 (43.9)	11 931 (35.1)
Current	17 (4.5)	2638 (7.8)
Alcohol consumption, No. (%)		
Never or past	73 (19.3)	5591 (16.5)
Current <1 drink/day	257 (68.0)	23 382 (68.9)
Current ≥1 drinks/day	48 (12.7)	4918 (14.5)
Duration of oral contraceptive use, No. (%)		
None	87 (23.0)	5171 (15.2)
<2 years	78 (20.6)	5007 (14.7)
2 to <10 years	152 (40.2)	14 476 (42.6)
≥10 years	60 (15.9)	9262 (27.3)
Hormone replacement therapy use, No. (%)[c]		
None	238 (63.0)	22 799 (67.2)
Estrogen alone	34 (9.0)	2329 (6.9)
Estrogen plus progestin	104 (27.5)	8736 (25.7)
Had worked in beauty salon or barbershop, No. (%)	11 (2.9)	1048 (3.1)

[a]Missing: age at menarche (29 overall), race and ethnicity (2 overall), education (5 overall), body mass index (11 overall), physical activity (3 cases, 269 overall), menopausal status at baseline (7 overall), parity (1 case, 23 overall), smoking status (8 overall), alcohol consumption (56 overall), oral contraceptive use (1 case, 31 overall), hormone replacement therapy (2 cases, 83 overall), and had worked in beauty salon or barbershop (1 case, 51 overall).
[b]Excluded women who withdrew (n = 3), were diagnosed with uterine cancer before baseline (n = 380), had an uncertain uterine cancer history (n = 10), had an unclear timing of diagnosis relative to enrollment (n = 59), had a hysterectomy prior to enrollment (n = 15 585), did not respond to all questions about hair product use (n = 736), or did not contribute any follow-up time (n = 164).
[c]The women who ever reported using estrogen-alone hormone replacement therapy were categorized as estrogen alone.

cancer. These findings are consistent with prior studies supporting a role of straighteners in increased risk of other female, hormone-related cancers (14,15,17-19,22).

To our knowledge, this is the first epidemiologic study investigating the relationship between straightener use and uterine cancer. Previous studies have demonstrated that exposure to straighteners was associated with lower sex steroid hormone levels (47,48), elevated risk of uterine leiomyomata (49), early age at menarche (50), and incident breast (14,15,17,19) and ovarian cancer (22), supporting a potential role of straighteners in the etiology of hormone-sensitive health outcomes.

Several chemicals often identified as constituents in straighteners (6,26,51,52) could contribute to the increased incident uterine cancer rates observed here. Concentrations of parabens in endometrium tissues and phthalates in urine samples were higher in participants with endometrial cancer than those who are endometrial cancer-free (53,54). Chronic exposure to low-dose bisphenol A has been associated with altered estrous

Table 2. Associations between ever use of hair product in the 12 months prior to enrollment and uterine cancer in the Sister Study

Hair product use[a]	Person-years	Full cohort No. (%)[b]	Case No. (%)[b]	Age-adjusted HR (95% CI)[c]	Fully adjusted HR (95% CI)[c,d]
Permanent dyes					
Never	162 425	14 795 (44.4)	184 (49.9)	Referent	Referent
Ever	200 450	18 531 (55.6)	185 (50.1)	0.88 (0.71 to 1.08)	0.90 (0.74 to 1.11)
Never to others	337 846	30 935 (92.7)	352 (95.4)	Referent	Referent
Ever to others	25 530	2436 (7.3)	17 (4.6)	0.76 (0.47 to 1.23)	0.69 (0.42 to 1.14)
Semipermanent dyes					
Never	293 148	26 829 (80.5)	307 (82.7)	Referent	Referent
Ever	69 590	6484 (19.5)	64 (17.3)	0.94 (0.71 to 1.23)	0.94 (0.72 to 1.24)
Never to others	350 705	32 169 (96.5)	362 (97.6)	Referent	Referent
Ever to others	12 246	1162 (3.5)	9 (2.4)	0.85 (0.44 to 1.64)	0.78 (0.4 to 1.51)
Temporary dyes					
Never	334 730	30 666 (92.1)	333 (90.2)	Referent	Referent
Ever	27 967	2644 (7.9)	36 (9.8)	1.29 (0.91 to 1.81)	1.25 (0.88 to 1.78)
Bleach					
Never	321 325	29 464 (88.5)	340 (91.6)	Referent	Referent
Ever	41 196	3832 (11.5)	31 (8.4)	0.73 (0.50 to 1.05)	0.77 (0.53 to 1.11)
Highlights					
Never	245 613	22 598 (67.7)	279 (75.8)	Referent	Referent
Ever	117 912	10 792 (32.3)	89 (24.2)	0.77 (0.6 to 0.97)	0.86 (0.68 to 1.1)
Straighteners, relaxers, or pressing products					
Never	333 535	30 329 (90.9)	332 (89.7)	Referent	Referent
Ever	29 733	3036 (9.1)	38 (10.3)	1.63 (1.17 to 2.29)	1.80 (1.12 to 2.88)
Never to others	354 618	32 465 (97.3)	358 (97.0)	Referent	Referent
Ever to others	8775	914 (2.7)	11 (3.0)	1.76 (0.96 to 3.22)	1.42 (0.72 to 2.79)
Hair permanents or body waves					
Never	323 483	29 689 (89.0)	316 (85.6)	Referent	Referent
Ever	39 779	3681 (11.0)	53 (14.4)	1.13 (0.84 to 1.53)	1.01 (0.75 to 1.37)

[a]Missing: permanent dyes (2 cases, 137 overall); permanent dyes to others (2 cases, 92 overall); semipermanent dyes (150 overall); semipermanent dyes to others (132 overall); temporary dyes (2 cases, 153 overall); bleach (167 overall); highlights (3 cases, 73 overall); straighteners, relaxers, or pressing products (1 case, 98 overall); straighteners, relaxers, or pressing products to others (2 cases, 84 overall); hair permanents or body waves (2 cases, 93 overall). CI = confidence interval; HR = hazard ratio.

[b]Participants with complete confounder information.

[c]Accounted for age by using age as the timescale, where the participants were followed from age at baseline until age at end of follow-up.

[d]Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), education (high school or less, some college, college and above), body mass index (restricted cubic spline, continuous, kg/m^2), physical activity (metabolic equivalent [MET] hours per week, continuous), menopausal status at enrollment (premenopausal, postmenopausal), parity (0, 1, 2, ≥3), smoking (never, past, or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2 to <10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin but never estrogen alone), age at menarche (<13 years, ≥13 years old).

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cycle and uterine pathology in rats, which has been associated with endometrial cancer development and progression (7,9). Moreover, cyclosiloxanes have been associated with neoplastic responses in the uterus of rats (55-57), and diethanolamine, metals, and formaldehyde have been considered carcinogenic (9,25,27,58,59).

Notably, chemical exposure through the pathway of hair product use, especially straighteners, could be more concerning than other personal care products. Higher percutaneous absorption of chemicals has been observed in scalp compared with other skin such as on the forearm, palm, and abdomen (60). Straightener use may cause scalp lesions and burns, which facilitates the permeability of chemicals through the scalp (61,62). Heating processes such as flat ironing or blow drying during straightening treatments could release or thermally decompose chemicals from the products, leading to potential higher exposures to hazardous chemicals among the users (63,64).

We observed stronger associations with straightener use among women with low physical activity. Because physical activity has been associated with decreased sex steroid hormones and less chronic inflammation (65), women with higher physical activity might be less susceptible to other risk factors for uterine cancer. However, more studies are warranted to understand the interrelationship between physical activity, hair product use, and uterine cancer.

Obesity has previously been shown to modify associations between the exposures related to hormonal activity and uterine cancers (66-69); however, we did not observe heterogeneity by obesity. Although more estrogen and progesterone receptor–positive tumors have been observed in premenopausal than postmenopausal endometrial cancers (41,70), we did not observe a stronger effect of hair product use on premenopausal cases possibly because of a small number of exposed cases (n = 5). However, when we limited the outcome to hormone-sensitive (type I) cancer subtype, the effect estimates remained similar, supporting a potential hormonal mechanism linking hair product use to uterine cancer.

Although no differences in the hazard ratios between racial and ethnic groups were observed, the adverse health effects associated with straightener use could be more consequential for African American and/or Black women because of the higher prevalence and frequency of hair product use, younger age of initiating use, and harsher chemical formulations (ie, higher

Table 3. Association of hair product use frequency, color of dyes, and duration of use with uterine cancer in the Sister Study

Hair product use[a]	Person-years	Full cohort No. (%)[b]	Case No. (%)[b]	Age-adjusted HR (95% CI)[c]	Fully adjusted HR (95% CI)[c,d]
Permanent dyes					
Frequency in the past 12 months prior to baseline					
Never	162 425	14 795 (44.4)	184 (49.9)	Referent	Referent
≤4 times	83 284	7740 (23.2)	64 (17.3)	0.80 (0.60 to 1.06)	0.79 (0.59 to 1.05)
>4 times	117 166	10 791 (32.4)	121 (32.8)	0.92 (0.73 to 1.16)	0.98 (0.78 to 1.24)
P_{trend}[e]				.44	.77
Color used in the past 12 months prior to baseline					
Never	162 425	14 795 (44.4)	184 (49.9)	Referent	Referent
Light color[f]	107 507	9895 (29.6)	98 (26.5)	0.87 (0.69 to 1.10)	0.93 (0.73 to 1.18)
Dark color[f]	111 846	10 401 (31.2)	101 (27.4)	0.92 (0.72 to 1.16)	0.91 (0.72 to 1.16)
Duration of use, lifetime					
Never	128 528	11 660 (35.4)	151 (41.8)	Referent	Referent
<5 years	61 572	5688 (17.3)	48 (13.3)	0.76 (0.55 to 1.06)	0.75 (0.54 to 1.04)
5 to <10 years	55 141	5064 (15.4)	50 (13.9)	0.83 (0.60 to 1.14)	0.84 (0.61 to 1.15)
≥10 years	113 108	10 494 (31.9)	112 (31.0)	0.80 (0.63 to 1.03)	0.82 (0.64 to 1.05)
P_{trend}[e]				.10	.14
Semipermanent dyes					
Frequency in the past 12 months prior to baseline					
Never	293 148	26 829 (80.5)	307 (82.7)	Referent	Referent
≤4 times	41 738	3903 (11.7)	35 (9.4)	0.92 (0.65 to 1.31)	0.91 (0.63 to 1.29)
>4 times	27 852	2581 (7.7)	29 (7.8)	0.96 (0.65 to 1.40)	0.98 (0.67 to 1.44)
P_{trend}[e]				.69	.77
Color used in the past 12 months prior to baseline					
Never	293 148	26 829 (80.5)	307 (82.7)	Referent	Referent
Light color[f]	25 324	2339 (7.0)	19 (5.1)	0.72 (0.45 to 1.14)	0.73 (0.46 to 1.17)
Dark color[f]	46 522	4364 (13.1)	44 (11.9)	1.02 (0.74 to 1.40)	1.03 (0.74 to 1.42)
Duration of use, lifetime					
Never	249 458	22 877 (70.1)	254 (71.1)	Referent	Referent
<5 years	54 979	5014 (15.4)	49 (13.7)	0.94 (0.69 to 1.27)	0.93 (0.69 to 1.27)
5 to <10 years	25 424	2326 (7.1)	28 (7.8)	1.08 (0.73 to 1.60)	1.15 (0.78 to 1.70)
≥10 years	25 570	2414 (7.4)	26 (7.3)	0.91 (0.61 to 1.36)	0.90 (0.60 to 1.35)
P_{trend}[e]				.78	.85
Straighteners, relaxers, or pressing products					
Frequency in the past 12 months prior to baseline					
Never	333 535	30 329 (90.9)	332 (89.7)	Referent	Referent
≤4 times	14 268	1464 (4.4)	12 (3.2)	1.06 (0.59 to 1.88)	1.20 (0.63 to 2.29)
>4 times	15 464	1572 (4.7)	26 (7.0)	2.19 (1.47 to 3.26)	2.55 (1.46 to 4.45)
P_{trend}[e]				<.001	.002
Hair permanents or body waves					
Frequency in the past 12 months prior to baseline					
Never	323 483	29 689 (89.0)	316 (85.6)	Referent	Referent
≤2 times	21 293	1951 (5.8)	23 (6.2)	0.99 (0.65 to 1.52)	0.92 (0.60 to 1.41)
>2 times	18 486	1730 (5.2)	30 (8.1)	1.28 (0.87 to 1.89)	1.11 (0.75 to 1.63)
P_{trend}[e]				.24	.71

[a]Missing: permanent dyes (2 cases, 137 overall); color of permanent dyes (4 cases, 168 overall); duration of permanent dye uses (10 cases, 557 overall); semipermanent dyes (150 overall); color of semipermanent dyes (2 cases, 172 overall); duration of semipermanent dyes use (14 cases, 832 overall); straighteners, relaxers, or pressing products (1 case, 98 overall); hair permanents or body waves (2 cases, 93 overall). CI = confidence interval; HR = hazard ratio.

[b]Participants with complete confounder information.

[c]Accounted for age by using age as the timescale, where the participants were followed from age at baseline until age at end of follow-up.

[d]Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), education (high school or less, some college, college and above), body mass index (restricted cubic spline, continuous, kg/m^2), physical activity (metabolic equivalent [MET] hours per week, continuous), menopausal status at enrollment (premenopausal, postmenopausal), parity (0, 1, 2, ≥3), smoking (never, past, or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2 to <10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin but never estrogen alone), age at menarche (<13 years, ≥13 years old).

[e]Assessed using Wald tests for continuous variables of hair product use frequency and duration.

[f]Hair color is nonexclusive: participants could be both light and dark users. Both colors were included in the models simultaneously.

concentrations of EDCs and chemicals being regulated or banned) than other races and ethnicities (6,71).

Strengths of this study include the prospective cohort design and access to medical records for most cases, which reduced the possibility of recall bias and allowed investigation by different uterine cancer subtypes. Brands or ingredients of hair products were not collected; thus, the specific chemicals contributing to incident uterine cancer were not identified. However, because some products may be regularly applied, our approach has the benefit of capturing chronic exposures to chemicals

Table 4. Association between hair product use in the 12 months prior to enrollment and uterine cancer by subtypes

Hair product use[a]	Ever		Frequent[b]		
	Case No. (%)[c]	HR (95% CI)[d]	Case No. (%)[c]	HR (95% CI)[d]	P_{trend}[e]
Permanent dyes					
Premenopausal cases[f]	12 (50.0)	0.66 (0.29 to 1.48)	7 (29.2)	0.82 (0.32 to 2.13)	.61
Postmenopausal cases[f]	173 (50.1)	0.95 (0.76 to 1.18)	114 (33.0)	1.00 (0.79 to 1.28)	.96
Medically confirmed cases[g]					
All uterine cancer	123 (47.9)	0.80 (0.63 to 1.03)	86 (33.5)	0.92 (0.70 to 1.21)	.44
Endometrial cancer[h]	119 (49.0)	0.83 (0.64 to 1.06)	83 (34.2)	0.94 (0.71 to 1.24)	.56
Type I endometrial cancer[i]	97 (49.7)	0.83 (0.62 to 1.10)	72 (36.9)	1.01 (0.74 to 1.37)	.92
Type II endometrial cancer[j]	19 (48.7)	0.90 (0.48 to 1.70)	11 (28.2)	0.80 (0.38 to 1.69)	.58
Semipermanent dyes					
Premenopausal cases[f]	5 (20.8)	0.89 (0.33 to 2.41)	1 (4.2)	—[k]	—[k]
Postmenopausal cases[f]	59 (17.0)	0.98 (0.73 to 1.31)	28 (8.1)	1.05 (0.71 to 1.55)	.97
Medically confirmed cases[g]					
All uterine cancer	44 (17.1)	0.98 (0.70 to 1.36)	20 (7.8)	1.02 (0.65 to 1.62)	.98
Endometrial cancer[h]	39 (16.0)	0.92 (0.65 to 1.30)	17 (7.0)	0.93 (0.56 to 1.52)	.67
Type I endometrial cancer[i]	33 (16.8)	0.98 (0.67 to 1.43)	15 (7.7)	1.05 (0.62 to 1.79)	.98
Type II endometrial cancer[j]	5 (12.8)	0.73 (0.28 to 1.88)	2 (5.1)	—[k]	—[k]
Straighteners, relaxers, or pressing products					
Premenopausal cases[f]	5 (20.8)	1.56 (0.26 to 9.29)	5 (2.08)	1.56 (0.26 to 9.29)	—[l]
Postmenopausal cases[f]	33 (9.5)	1.90 (1.16 to 3.13)	21 (6.1)	2.52 (1.39 to 4.55)	.003
Medically confirmed cases[g]					
All uterine cancer	21 (8.2)	1.94 (1.10 to 3.42)	14 (5.4)	2.78 (1.39 to 5.55)	.005
Endometrial cancer[h]	17 (7.0)	1.89 (1.04 to 3.43)	11 (4.5)	2.68 (1.30 to 5.53)	.005
Type I endometrial cancer[i]	13 (6.7)	1.89 (1.01 to 3.54)	9 (4.6)	2.94 (1.42 to 6.08)	.009
Type II endometrial cancer[j]	2 (5.1)	—[k]	2 (5.1)	—[k]	—[k]
Hair permanents or body waves					
Premenopausal cases[f]	4 (15.7)	—[k]	3 (12.5)	—[k]	—[k]
Postmenopausal cases[f]	49 (14.2)	0.96 (0.69 to 1.32)	27 (7.8)	0.96 (0.63 to 1.46)	.80
Medically confirmed cases[g]					
All uterine cancer	33 (12.8)	0.93 (0.64 to 1.36)	19 (7.4)	1.07 (0.66 to 1.74)	.95
Endometrial cancer[h]	31 (12.8)	0.94 (0.64 to 1.39)	19 (7.8)	1.18 (0.72 to 1.92)	.87
Type I endometrial cancer[i]	26 (13.3)	1.04 (0.68 to 1.59)	16 (8.2)	1.36 (0.80 to 2.32)	.51
Type II endometrial cancer[j]	5 (12.8)	0.82 (0.31 to 2.16)	3 (7.7)	—[k]	—[k]

[a]Missing: permanent dyes (2 cases, 137 overall); semipermanent dyes (150 overall); straighteners, relaxers, or pressing products (1 case, 98 overall); hair permanents or body waves (2 cases, 93 overall). CI = confidence interval; HR = hazard ratio.
[b]Definition of frequent use: >4 times in the past 12 months (permanent dyes; semipermanent dyes; straighteners, relaxers, or pressing products); >2 times in the past 12 months (hair permanents or body waves).
[c]Participants with complete confounder information. Percentage of ever or frequent users among cases.
[d]Compared with never users. Adjusted for race and ethnicity (African American and/or Black, Hispanic and/or Latina non-Black, non-Hispanic White, other), education (high school or less, some college, college and above), body mass index (restricted cubic spline, continuous, kg/m^2), physical activity (metabolic equivalent [MET] hours per week, continuous), menopausal status at enrollment (premenopausal, postmenopausal), parity (0, 1, 2, ≥3), smoking (never, past, or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2 to <10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin but never estrogen alone), age at menarche (<13 years, ≥13 years old).
[e]Assessed using Wald tests for continuous variables of hair product use frequency (never, infrequent, frequent use).
[f]Person-time is stratified by menopausal status.
[g]Confirmed diagnosis with medical records or death certificates from National Death Index (NDI).
[h]*International Classification of Disease* (ICD)–10 code of C54.1 = malignant neoplasm of endometrium.
[i]ICD-Oncology-3 histology codes: 8140, 8262, 8380, 8382, 8480, 8560, and 8570.
[j]ICD-Oncology-3 histology codes: 8310, 8323, 8441, 8460, 8950, and 8980.
[k]Data not presented as small number of cases (<5) within any stratum in the model.
[l]Unable to assess P_{trend} because all cases are frequent users.

with short biological half-lives, which would be challenging to assess using biomarkers in relation to an outcome like cancer with a long latent period. Further, self-reported hair product use reflects exposure to chemical mixtures including chemicals that have not been previously identified (47). We evaluated exposure in the 12 months before the baseline; however, product use behaviors and product formulations may vary over time. In the questionnaire, straightening product use was inclusive of use of pressing products. Because pressing hair is a treatment using heated combs and/or flatirons, which requires less harsh products than chemical straighteners and relaxers, the estimated associations might underestimate the true relationship between the use of chemical straighteners and relaxers and uterine cancer.

In this large, prospective cohort study, we observed that straightening product use was positively associated with uterine cancer. More research is warranted to confirm our novel findings in different populations, particularly in African American and/or Black women because of the high prevalence of straightener use, and to evaluate the potential contribution

Table 5. Associations between straightener, relaxer, or pressing products use in the 12 months prior to enrollment and uterine cancer in the Sister Study stratified by participant characteristics

	Ever		Frequent[b]		
Potential modifier[a]	Case No. (%)[c]	HR (95% CI)[d]	Case No. (%)[c]	HR (95% CI)[d]	P_{trend}[e]
Race and ethnicity[f]					
African American/Black[g]	23 (79.3)	1.66 (0.67 to 4.09)	17 (58.6)	2.12 (0.83 to 5.39)	.09
Non-Hispanic White	12 (3.8)	1.94 (1.09 to 3.47)	7 (2.2)	2.66 (1.25 to 5.67)	.011
$P_{heterogeneity}$[h]		.77		.71	
BMI					
Nonobese (<30 kg/m^2)	16 (7.7)	1.81 (1.04 to 3.17)	10 (5.1)	2.48 (1.22 to 5.03)	.010
Obese (≥30 kg/m^2)	22 (12.6)	1.68 (0.90 to 3.14)	16 (9.2)	2.40 (1.19 to 4.85)	.022
$P_{heterogeneity}$[h]		.83		.94	
Physical activity[i]					
Low	22 (15.3)	2.59 (1.46 to 4.61)	15 (10.4)	3.72 (1.91 to 7.25)	<.001
High	16 (7.1)	1.30 (0.71 to 2.38)	11 (4.9)	1.86 (0.89 to 3.87)	.16
$P_{heterogeneity}$[h]		.05		.09	

[a]Missing: straighteners, relaxers, or pressing products (1 case, 98 overall). BMI = body mass index; CI = confidence interval; HR = hazard ratio.
[b]Definition of frequent use: >4 times in the past 12 months (permanent dyes; semipermanent dyes; and straighteners, relaxers, or pressing products).
[c]Participants with complete confounder information. Percentage of ever or frequent users among cases in each stratum.
[d]Compared with never users. Accounted for age by using age as the timescale, where the participants were followed from age at baseline until age at end of follow-up. Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), education (high school or less, some college, college and above), BMI (restricted cubic spline, continuous, kg/m^2), physical activity (metabolic equivalent [MET] hours per week, continuous), menopausal status at enrollment (premenopausal, postmenopausal), parity (0, 1, 2, ≥3), smoking (never, past, or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2 to <10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin but never estrogen alone), age at menarche (<13 years, ≥13 years old).
[e]Assessed using Wald tests for continuous variables of hair product use frequency (never, infrequent, frequent use).
[f]Non-Black Hispanic or other race and ethnicity were excluded because of small sample size and limited power.
[g]Including Hispanic and Latina Black.
[h]Assessed using Wald tests for hair product-by-modifier interaction terms.
[i]Low and high physical activities were categorized by 33rd percentile 32.7 MET hours per week.

of hair products to health disparities in uterine cancer. Future efforts are also needed to identify the chemical ingredients, which might result in the elevated rates. Given the widespread use of hair products and the rising incidence of uterine cancer (2), our findings which identify hair straightener use as a potential target for intervention are particularly relevant for public health approaches to reduce uterine cancer incidence.

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Data Availability

All data necessary to reproduce the current analysis are publicly available following procedures described on the Sister Study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

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